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(54) DIP COATING PROCESS FOR PREPARING CELLULOSE ETHER FILM PRODUCTS

(71) We, THE DOW CHEMICAL COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of Midland, County of Midland, State of Michigan, United States of America do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Pharmaceutical capsule shells have long been made of gelatin in spite of the recognized deficiencies of gelatin shells at very low or high humidity. No other material has yet met the rigid requirements for commercial acceptance.

Water-soluble, film-forming cellulose ethers have been suggested. Thus, in U.S. Patent 2,526,683, issued October 24, 1950, Murphy describes the preparation of methyl-cellulose capsules by a process involving thermal gelation of an aqueous cellulose ether solution on a preheated capsule forming pin. Greminger and Weaver in U.S. Patent 2,810,659, issued October 22, 1957, describe plasticized cellulose ether compositions suitable for molding or extruding into flexible films and capsules. However, mechanical problems and poor capsule properties have prevented commercial use of these processes.

A dip coating process has now been discovered in which elimination of thermal gelation in the coating bath, use of certain low viscosity hydroxyalkyl cellulose ethers, and rapid immobilization of the dip coating by induction heating after removal from the coating bath are critical elements. More specifically, the process comprises: (A) Dipping a die mandrel having an electrically conductive outer surface and a surface temperature below the gel point temperature of the coating solution into an aqueous thermal gelling coating solution having a viscosity of 1000—12,000 cps and containing at least 20 wt% of a film-forming C_2 — C_4 hydroxy-

alkyl C_1 — C_2 alkyl cellulose ether having a hydroxyalkyl M.S. of 0.07—1.0, an alkyl D.S. of 0.6—2.0, and a viscosity of 2—20 cps as a 2 wt% aqueous solution at 20°C; (B) Removing the coated die mandrel from the aqueous coating solution; (C) Rapidly converting the cellulose ether coating into a non-flowing gel by induction heating; and thereafter (D) Drying the gelled coating to form a stable cellulose ether film product.

By preventing thermal gelation in the dip coating bath, a more uniform, clean breaking coating of the die mandrel is obtained. But once removed from the bath, the cellulose ether coating is rapidly gelled by induction heating to provide a stable, non-flowing and uniform coating. Final drying provides a hard and strong cellulose ether film product quite suitable for pharmaceutical applications. These products have good film clarity and rate of dissolution, yet they remain firm and sturdy under conditions of extreme humidity.

Murphy, in U.S. Patent 2,526,683, previously identified, describes the general requirements for an aqueous dip coating bath of a thermal gelling cellulose ether. To obtain a dry film thickness of about 4—5 mils in a single dip operation, the bath must contain at least 20 wt% of the cellulose ether and have an operational viscosity of 1,000—12,000 cps. This requires a water-soluble cellulose ether with a standard 2% by weight aqueous solution viscosity of 2—20 cps at 20°C, preferably 2—7 cps. Particularly effective is a bath having a viscosity of 1,000—4,000 cps at a dip coating temperature of 25°—35°C.

Typical of the water-soluble, film-forming cellulose ethers used herein are hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, and hydroxyethyl ethyl cellulose. The cellulose ethers for use in this invention have a C_2 — C_4 hydroxyalkyl M.S. of 0.07—1.0 and a C_1 — C_2 alkyl D.S. of 0.6—2.0. Most desirable for pharmaceutical applications because of film clarity and water solubility are cellulose ethers having a hydroxy-

propyl M.S. of 0.15—0.35 and a methyl D.S. of 1.8—2.0. The terms M.S. (molar substitution) and D.S. (degree of substitution) are used as defined in Klug U.S. Patent 3,357,971, issued December 12, 1967. In a preferred embodiment of the invention the coating solution contains 25—35 wt% of the hydroxypropylmethyl cellulose ether and has a viscosity of 1,000—4,000 cps at the dip coating temperature.

These thermal gelling hydroxyalkyl alkyl cellulose ethers normally have an aqueous 2% solution gel point of 45°—90°C. as determined from a standard temperature-viscosity curve. [Cf. A. B. Savage, Ind. and Eng. Chem. 49 99(1957).] The more concentrated aqueous solutions used in the present process have gel points normally 10°—20° lower than the 2% solutions. Stiff, immobilized and non-flowing gels are obtained when the concentrated aqueous solution is heated to a few degrees above its gel point. For example, a hydroxypropyl methyl cellulose with a 27% solution gel point of about 60°C. as a 25% solution has a gel of about 42°C. and forms a firm non-flowing gel at 45—46°C. Further control of the dip coating solution gel point can be obtained using conventional cellulose ether gelation additives such NaCl, Na₂SO₄, Na₂CO₃, Na₃PO₄, MgCl₂, Al₂(SO₄)₃ or urea.

Normally the temperature of the dip coating bath is held about 5°—10°C. below its gel point temperature. Under these conditions effective dip coating is obtained by immersing a die mandrel having a surface temperature below the thermal gel point of the bath into the bath and then smoothly removing the coated die from the bath allowing the excess coating solution to drain from the die as it separates from the bath.

A critical element in the present process is the rapid immobilization of the cellulose ether coating after removal from the dip coating bath. Unless the coating is rapidly immobilized on the die surface, the coating uniformity will be lost with formation of flow bulges or tyres. Particularly in preparing pharmaceutical capsule shells, extreme coating uniformity is required.

Attempts to immobilize the coating by conventional heating methods using preheated air, infra-red heaters, dielectric heaters, electric resistance heaters, all failed to provide the requisite rapid, direct and flexible heating required for a commercial dip coating operation. However, induction heating was found to be highly effective giving gelation and immobilization of the coating in a few seconds.

Induction heating uses a skin-effect phenomena observed when an electroconductive object is placed within an electromagnetic field formed by the flow of rapidly alternating current in a coil. As applied to the dip

coating process, the coated die mandrel immediately after removal from the cellulose ether bath passes into an induction heater unit. The electric currents induced in the die mandrel heat its surface and rapidly raise the temperature of the aqueous cellulose ether coating above its gel point. Thus the coating is effectively and rapidly immobilized. Thereafter further drying of the gelled coating can be carried out by any desired method without distortion of the coating film, a critical requirement in producing capsule shells.

To permit induction heating, the die mandrel must have an outer surface of an electrically conductive metal such as aluminum, brass, copper, steel or titanium. Magnetic metals are particularly effective since the magnetic permeability generally results in higher induction heating surface temperatures. Particularly suitable in the manufacture of capsule shells are stainless steel pins which can be machined to a close tolerance and mounted on a non-conductive support.

A suitable induction heater comprises a copper coil energized by a single phase alternating current. In general, a frequency range of 200—5,000 kilocycles per second, preferably 250—400 kc/sec., is suitable for rapid gelation of the cellulose ether dip coating. Further details on induction heating of conductive metals are given in Faulkner U.S. Patent 2,902,572, issued September 1, 1959, and Alf U.S. Patent 3,041,434, issued June 26, 1962, for example.

Since the induced currents are concentrated near the surface of the die mandrel, it becomes a highly efficient and selective heating source for the thermal gelation of the cellulose ether. A further advantage of the induction heater is that no physical contact is required between the energy source and the object to be heated, thus lending flexibility to the system design and operation.

By appropriate control of the frequency and field strength, effective thermal gelation can be achieved in about 1—30 sec. Thereafter the gelled cellulose ether coating held at a temperature above its gel point can be dried in any convenient manner, such as a hot air kiln, until a firm, essentially water free film or coating is obtained. In the production of pharmaceutical capsules, the dried cellulose ether capsule shells are removed from the die mandrel, trimmed and assembled.

Normally the cellulose ether films or coatings are relatively clear and transparent. However, if opaque capsules are desired, a minor amount of inert non-toxic pigment such as powdered charcoal or finely divided titanium dioxide can be incorporated in the coating composition. Conventional non-toxic dyes and fillers can also be used. For increased flexibility, an appropriate plasti-

cizer such as glycerine, propylene glycol, or hydroxypropyl glycerine can be included in a moderate amount, e.g., 5 to 20% by weight.

This process is particularly suited for preparing pharmaceutical capsule shells which dissolve at a rate comparable to gelatin capsules. Delay release characteristics can be obtained by incorporation of a less water-soluble cellulose ether such as ethyl cellulose as described by Greminger and Windover in U.S. Patent 2,887,440, issued May 19, 1959.

To illustrate further the present invention, the following examples are given. Unless otherwise specified, all parts and percentages are by weight. Solution viscosities are determined by the method of ASTM D-1347-64 unless otherwise stated.

EXAMPLE 1

A. An aqueous dip coating solution was prepared by dissolving 250 parts of hydroxypropyl methyl cellulose in 750 parts water at room temperature. The hydroxypropyl methyl cellulose used had a 2% aqueous solution viscosity of 5 cps at 20°C. and a thermal gel point of 60°C. Its hydroxypropyl M.S. was 0.15—0.35 and its methyl D.S. 1.8—2.0. The clear 25% aqueous solution had a viscosity of 3,500 cps at 25°C. measured at a shear rate of 30 sec.⁻¹ on a Haake Rotovisco viscometer. Its gel point was 41—42°C. with a firm, rigid gel being obtained at 43—45°C.

B. Capsule shells were prepared from this aqueous cellulose ether solution using capsule pins machined from stainless steel and lightly coated with a cottonseed oil lubricant grease. The pins, mounted on a non-electrically conducting bar, were dipped into the cellulose ether solution at room temperature for 10—15 seconds. Then they were smoothly withdrawn from the solution allowing the excess to strip from the coated pin.

The coated pins were then immediately inverted and placed in a 5-kilowatt induction heater coil 15 cm long and 10 cm in diameter and consisting of 12 turns of 6—8 mm copper tubing connected to a 450 kilocycle per second alternating current source. In less than 20 seconds, the cellulose ether coating had gelled to an immobile form. Final drying was achieved in a warm air oven at 50°—60°C.

The resulting capsule shells stripped from the pins had a uniform thickness of 4 mils (0.102 mm.) with excellent retention of shape. No significant formation of thick rings or "tyres" from excessive rundown prior to gelation was observed. The shells were easily assembled into capsules. Their dried equilibrium water content was 5 wt% at room temperature and humidity.

EXAMPLE 2

In another test, the 25% aqueous hydroxypropyl methyl cellulose solution described in

Example 1 was modified by addition of 1.1 wt% sodium sulfate to give a solution with a gel point of 33°C. Capsule shells prepared from this solution turned opaque when gelled by induction heating and remained opaque when dry. Their dried shell thickness and shape were very uniform.

EXAMPLE 3

Further tests with a 5-kilowatt induction heater indicated that with continuous application of power, an immobile gel was obtained in 5—10 seconds. Other thermal gelling hydroxyalkyl alkyl cellulose ethers applied as 20—40 weight percent aqueous solutions gave similar results when the die mandrels were placed in an induction heater coil after dip coating.

WHAT WE CLAIM IS:—

1. A process for preparing cellulose ether products which process comprises dipping a die mandrel having an electrically conductive outer surface and a surface temperature below the gel point temperature of the coating solution into an aqueous thermal gelling coating solution having a viscosity of 1,000—12,000 cps and containing at least 20 wt% of a film-forming C₂—C₄ hydroxyalkyl C₁—C₃ alkyl cellulose ether having a hydroxyalkyl M.S. of 0.07—1.0, an alkyl D.S. of 0.6—2.0, and a viscosity of 2—20 cps as a 2 wt% aqueous solution at 20°C; removing the coated die mandrel from the aqueous coating solution; converting the cellulose ether coating into a non-flowing gel by induction heating; and thereafter drying the gelled coating to form a stable cellulose ether film product.
2. A process as claimed in claim 1 wherein the cellulose ether has a 2% aqueous solution viscosity of 2—7 cps.
3. A process as claimed in claim 1 or 2 wherein the aqueous, thermal gelling coating solution has a viscosity of 1,000—4,000 cps. at a dip coating temperature of 25—35°C.
4. A process as claimed in any of claims 1 to 3 wherein the cellulose ether is a hydroxypropylmethyl cellulose ether having a hydroxypropyl M.S. of 0.15—0.35, a methyl D.S. of 1.8—2.0, and a 2% aqueous solution viscosity of 2—7 cps at 20°C.
5. A process as claimed in any of claims 1 to 4 wherein the coating solution contains 25—35 wt% of the hydroxypropylmethyl cellulose ether and has a viscosity of 1,000—4,000 cps at the dip coating temperature.
6. A process as claimed in any of claims 1 to 5 wherein the die mandrel is made of stainless steel.
7. A process as claimed in any of claims 1 to 6 wherein the induction heater operates at a frequency of 200—5000 kilocycles per second.
8. A process as claimed in any of claims 1 to 6 wherein the induction heater operates at a frequency of 250—400 Kc/sec.

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9. A process for preparing pharmaceutical cellulose ether capsules by dip coating a stainless steel die mandrel into a 25—35 wt% aqueous solution of a hydroxypropylmethyl cellulose ether having a hydroxypropyl M.S. of 0.15—0.35, a methyl D.S. of 1.8—2.0, and a 2% aqueous solution viscosity of 2—7 cps at 20°C.; removing the coated die mandrel from the cellulose ether solution; rapidly converting the cellulose ether coating into a non-flowing gel by induction heating in a magnetic field generated by an induction heating coil operating at a frequency of 200—5,000 kilocycles per second; drying the gelled cellulose ether coating in a hot air oven; and stripping the capsule shell from the die mandrel.
10. A process for preparing cellulose ether products substantially as hereinbefore

described with reference to Examples 1 to 3. 20

11. A cellulose ether product whenever prepared by a process as claimed in any of claims 1 to 10.

12. Hydroxypropylmethyl cellulose ether pharmaceutical capsules whenever prepared by a process as claimed in any of claims 1 to 10. 25

13. A cellulose ether product as claimed in claim 11 in the form of a pharmaceutical capsule. 30

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